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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/192,064	11/13/1998	HARTOUN HARTOUNIAN	07333/043001	9320

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MASTERMIND IP LAW PC
421-A SANTA MARINA COURT
ESCONDIDO, CA 92029

EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 11/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/192,064	HARTOUNIAN ET AL.	
	Examiner	Art Unit	
	Gollamudi S Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-35,49 and 51-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 12-35, 49 and 51-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment and the request for the change of power of attorney dated 9-7-04 are acknowledged.

Claims included in the prosecution are 1-10, 12-35, 49 and 51-89.

Claim Rejections - 35 U.S.C. ' 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-10, 12-35, 49 and 51-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (cancer Treatment Reports, 1987) or Assil (arch. Ophthalmol. 1987) or Bonetti (Cancer Chemother. Pharmacol., 1994) or Kim (5,723,147), or Sankaram (5,766,627) in view of Lenk (5,48,441).

The above references of Kim, 1987, Assil, 1987, Bonetti 1994 or Kim 147 or Sankaram, 627 all teach basically the same process of preparation of multivesicular liposomes.

The process involves dissolving the amphipathic lipid and the neutral lipid in chloroform and mixing it with an aqueous solution containing sucrose and forming an emulsion (instant step A), mixing this emulsion with an aqueous solution (step b) and removing the organic solvent and thereby forming the multivesicular liposomes (note the experimental sections in the publications and examples in Kim 147 and Sankaram 627).

What are lacking in these references are the teachings of filtration by cross-flow filtration method and making a sterile preparation.

Lenk while disclosing a method for size separation of particles teaches that there are problems associated with various methods previously available for the preparation of liposomes or vesicles of a select size and that by the cross-filtration method (also called as tangential flow filtration method) allows one to select large quantities of liposomes of a homogeneous, defined size distribution from a heterogeneously-sized population (note the abstract, col. 4, line 12 through col. 6, line 49). Lenk also discloses preparations for various modes of administration and sterile solutions (note col. 15, lines 1-19 and examples).

The use of cross-flow filtration step in the method of preparation of multivesicular lipid particles of Kim, Assil, Bonetti or Sankaram would have been obvious to one of ordinary skill in the art since Lenk teaches the advantages of using such a step in the preparation of vesicles or liposomes. It is deemed within the skill of the highly developed

sciences to prepare a sterile preparation. It is also within the skill of the art to realize that if any composition is given by a systemic route, in the form of an injection in particular, that the preparation should be sterilized. Furthermore, it is clearly evident from Lenk that sterile preparations have to be used if they are administered to mammals. The criticality of the type of mixers and various method parameters recited in instant claims is not readily apparent to the examiner. In the absence of unexpected and unobvious results, these are deemed to be parameters manipulated by an artisan to obtain the best possible results. It is common practice in any field to perform a pilot method and extend it to a large-scale production.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the claims recite two limitations that are not disclosed in any of the primary references. The first limitation relates to forming a composition having a pre-determined, uniform size distribution." The second limitation relates to using cross-flow filtration for adjusting the concentration of the multivesicular liposomal particle composition." It is not merely cross flow filtration in and of itself that is missing from the primary references, as asserted by the Examiner. Rather, it is the novel use of cross-flow filtration for the particular process steps for which it is applied. These arguments are not found to be persuasive. With regard to the first issue: instant claims do not recite what the predetermined uniform sizes are in terms of diameters. Since the prior art teaches the same step (d in claim 1 for instance), one can say that the sizes achieved by this step in the prior art are predetermined sizes set forth by those inventors. Secondly, it is unclear to the examiner how one can predetermine the sizes

by solvent removal alone. With regard to the second issue: according to applicant, the primary references each disclose centrifugation as a means for adjusting the final concentration of the multivesicular liposome compositions disclosed therein, and for removing any unwanted buffer and unencapsulated drug and that the present invention discloses a novel process whereby cross-flow filtration is used to obtain those objectives, thereby resulting in higher yield and decreased process time. This argument is not found to be persuasive since Lenk precisely teaches these advantages on col. 7, lines 7-34. The final goal in Lenk and instant invention is to achieve these objectives and according to Lenk on col. 4, lines 12-20, the control of the particle sizes is achieved through tangential flow filtration is commercially important process and whether it is achieved in the final step by cross-flow filtration along with other benefits of this filtration step as taught by Lenk or select the size before are manipulatable parameters since end result is the same. With regard to increase of 8.4 % overall yield or reduction in process time as argued by applicant, it is the examiner's position that these are to be expected by the step taught by Lenk. Furthermore, at the location pointed out (page 53, lines 6-7) applicant states, "The step yield for adjustment by secondary cross-flow filtration was 96.9% (standard deviation of 2.7%), while the step yield for adjustment by decanting was 92.8% (standard deviation 3.4%). Thus, there is an 8.4% improvement in overall yield

associated with the use of secondary cross-flow filtration as an adjustment step". The difference appears to be 4.1 (96.9 – 92.8) and not 8.4 %. Irrespective of whether the

increase in yield is 4.1 or 8.4, it is the examiner's position that these are to be expected from Lenk's teachings of the advantages of using the cross-flow filtration.

While fully agreeing that it would be obvious to a person having ordinary skill in the at to prepare sterile compositions for injections, applicant argues that they do not cannot use filtration as a means for sterilization of the final liposome product due to the massive size of multivesicular liposomes. These arguments are not found to be persuasive since as pointed out in the previous actions, sterilizing the components used in a composition and preparing a composition under aseptic conditions or sterilizing the composition after it is prepared, when the compositions are meant for human administration, is well known in biological sciences; this is meant to avoid microbial contaminations. Secondly, applicant's own statement on page 5, lines 25-27 contradicts the present argument. At this location, applicant states, "The steps can be carried out aseptically, or the MVL can be sterilized before package filling is carried out. In either case, an MVL product results which is immediately suitable for administration in a subject" (see also page 19 of applicant's previous response dated 1-13-04). It is the examiner's position that this sterilization step is a manipulatable parameter.

3. Claims 1-10, 12-35, 49 and 51-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (cancer Treatment Reports, 1987) or Assil (arch. Ophthalmol. 1987) or Bonetti (Cancer Chemother. Pharmacol., 1994) or Kim (5,723,147) or Sankaram (5,766,627) in view of Lenk as set forth above, further in view of Kwasiborski (6,033,708), Fenski (5,837,282), Mehl

(5,885,260), Castor (5,776,486), Moynihan (5,589,189) by themselves or in combination.

The teachings of Kim, Assil, Bonetti, Sankaram and Lenk have been discussed above.

Kwasiborski (708) and Fenski (282) both teach a method of preparation of sterile liposome dispersion; the method involves filtering through 0.2 micron filters (note the examples and claims of Kwasiborski; col. 11, line 40 et seq.).

Mehl (260) while disclosing sterile liposome preparations teaches that administration to humans requires that the liposomes be pyrogen free and sterile and advocates the use of filters (note col. 3, line 54 et seq.).

Castor teaches the awareness in the art of sterilizing individual components and solutions and the filtration of liposomes (note col. 2, line 37 et seq.).

Moynihan teaches that the best method for terminal sterile filtration is the sequential filtration of dispersed liposomes (note col. 3, line 33 et seq.).

One of ordinary skill in the art would be motivated to prepare the multivesicular liposomes in a sterile state because the references of Kwasiborski, Fenski, Mehl, Castor and Moynihan each teach methods that involve the production of sterile liposomes and therefore, a similar sterile production of liposomes is to be expected with instant liposomes also.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that none of these references teach the control of the particle sizes in relation to energy input at the time of liposome formation and instant

method does not use sterilization via filtration techniques. These have been addressed above.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK